REMARKS

Re-examination and favorable reconsideration in light of the above amendments and the following comments are respectfully requested.

Claims 1 - 32 are pending in the application. Currently, claims 1 - 4, 10 - 18, and 26 - 32 stand rejected and claims 5 - 9 and 19 - 25 stand withdrawn as being directed to a non-elected invention.

By the present amendment, claims 1 - 4, 10 - 18, and 26 -32 have been amended. Further, new claims 33 - 35 have been added to the application.

The office action mailed March 24, 2003 contains numerous objections and rejections which will be discussed hereinafter.

The present invention relates to compositions for use in the treatment or the prevention of allergies. The technical problem set forth by the inventors is the global treatment of atopy by acting both on the symptoms and on the cause of the allergy.

The solution to this technical problem is to combine an anti-histaminic compound and an inhibitor of the synthesis of histamine with an allergen, especially an allergen peptide. Anti-histamine and inhibitors of synthesis of histamine are known, but the usual practice of

doctors is to use the two separately and not together. According to the invention, the anti-histaminic is used to block the fixation of histamine on the H1 receptor, but (1) the combination of both anti-histaminic and inhibitor of histamine synthesis is meant to enhance the switch of TH2 to TH1 by blocking upstream the synthesis of histamine and therefore limiting the amount of histamine in the body (histamine is known to help prevailing the TH2 cells) and (2) the combination of anti-histaminic and inhibitor of histamine synthesis with a mono-allergen peptide turns the patient to a TH1 profile, and this happens whatever is the allergen responsible of the allergy. The allergen peptide is able to treat or prevent an allergy caused by another allergen. The compositions of the present invention are therefore useful for allergies caused by other allergen than the one present in the composition. The present invention leads to great results, which is due to the synergetic effect of the combined compounds present in the composition.

By the present amendment, claims 1 - 4, 10 - 18, and 26 - 32 have been amended to eliminate the objections made by the Examiner in paragraphs 5 - 9 of the office action.

With regard to the objection raised by paragraph 10, it is Applicants' belief that there is no requirement in

the Patent Office Rules or the Patent Laws which would require Applicants to amend the application to insert the fact that Applicants are claiming priority to two French patent applications. If the Examiner believes there is such a requirement or rule, he is hereby requested to cite same.

With respect to paragraphs 11 and 12 in said office action, a substitute specification is attached hereto. No new matter has been added to the substitute specification. The differences between the original specification and the substitute specification are only cosmetic and primarily grammatical in nature.

In paragraphs 14 and 15 of the office action, claims 1 - 4, 10 - 18, and 26 - 32 were rejected under 35 U.S.C. 112, first paragraph. Applicants submit that the instant specification fully complies with the disclosure and enablement requirements of 35 U.S.C. 112, first paragraph. To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *Genentech Inc. v. Novo Nordisk A/S*, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997). While every aspect of a generic claim need not have been carried out by an inventor, or exemplified in the specification, reasonable

detail must be provided in order to enable members of the public to understand and carry out the invention. *Genentech,* 42 USPQ2d at 1005. It is submitted that the specification in the instant application provides the reasonable details needed for one of ordinary skill in the art to understand and carry out the invention. In making the enablement rejection, the Examiner forgets that the level of skill in this area is very high and that anti-histamines and inhibitors of synthesis of histamines have been used in the art for many years. One skilled in the art is a manufacturer of pharmaceuticals for treating or preventing allergies. Such an individual has extended knowledge on allergens, anti-histamine compounds, and inhibitors of histamine synthesis - the three materials which are combined to form the compositions of the present invention.

Applicants concede that some experimentation may be needed for compounds unnamed in the specification; however, enablement is not precluded by the necessity for some experimentation. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Again, the specification in the instant application provides a reasonable amount of guidance with respect to the direction in which any experiment must proceed. In this regard, specific amounts of composition

components are provided along with the results of a test run by Applicants.

Applicants disagree with the Examiner's assessment of the *Wands* factor. The scope of the claim is appropriate in view of the disclosure in this case. Sufficient compounds, and the amounts needed to form the claimed compositions, are identified so that one of ordinary skill in the art can form the claimed invention. Thus, there is ample direction and guidance provided. As for the alleged lack of sufficient working examples, there is no requirement in the Patent Law that any examples be provided. However, given the depth of the disclosure in this case, it is not necessary to have a large number of examples. The Examiner alludes to the unpredictability of the art, yet fails to establish that the art is in fact so unpredictable that the specification is rendered non-enabling. As for the amount of experimentation, the Examiner has not established that an *undue* amount of experimentation is required. If the Examiner is going to rely on this factor, then the specific reasons why an undue amount of experimentation is needed should be stated in the rejection.

The use of more than one allergen peptide, in combination with the other compounds, has led to the results of the present invention. It is the simultaneous

action of the three functions (allergen, anti-histamine, and inhibitor of histamine synthesis) at several steps of the allergic reaction chain that causes the good results associated with the compounds of the present invention. One of ordinary skill in the art reading the instant disclosure and the claims wound readily understand this.

As to the Stryer, Ngo et al., and Fassler et al. patents mentioned by the Examiner, they are not probative on the issue of enablement. They are merely part of the technological background of the invention but do not teach or suggest the compositions of the present invention. The present invention does not relate to a definite sequence or compounds, but to a combination of compounds, each having a function. Thus, these patents really have nothing to say as to whether the instant specification is enabling.

With regard to the '345 patent, this patent teaches that anti-histamine compounds are symptomatic medicines, which treat the effects of allergy, but do not prevent the cause of the allergic reaction and the liberation of chemical mediators. According to the present invention however, it is the combination of anti-histaminic and of inhibitor of histamine which cooperate to prevent the remaining of high levels of histamine in the body and therefore, to prevent the liberation of chemical mediators

and the increase or remaining of the allergic symptoms. Thus, the '345 patent has no bearing on the issue of the enablement of the disclosure in the instant application.

As for the term "preventing", it should be noted that the term "prevention" is meant in the instant invention as (1) to avoid the first occurrence of an allergic reaction in a subject that has been tested and recognized as potentially allergic (2) to avoid a further occurrence of an allergic reaction in subject that has had one in the past. What is sought to be prevented is the occurrence and aggravation of the allergic reaction in an individual able to show such a reaction.

As to the selection or identification guidance which the Examiner seeks, it should be noted that the present invention is directed to compositions for preventing allergic reactions. How the individual is selected or identified is irrelevant to the issue of enablement. Test for identifying or selecting individuals prone to allergies are well known in the prior art.

In conclusion, one skilled in the art is well informed on the compounds having the claimed functions. The simultaneous action of these functions is the core of this invention and leads to the result of the invention, whatever the compounds are, provided that they show the

claimed functions. Carrying out the claimed invention is really easy for one skilled in the art having read the description in this application, because it only involves his/her general knowledge and a simple, novel, and unobvious combination of the compounds.

With respect to the rejection in paragraph 15 of the office action, the discussion on enablement is applicable here as well. The patent law does not require an inventor to disclose all possible compounds which may be used to carry out his/her invention. Sufficient guidance has been provided in the disclosure of the instant application to allow one of ordinary skill in the art to make and use the claimed invention. The examiner is far too focused on the word "any" to recognize that the disclosure in the instant specification provides sufficient guidance for one of ordinary skill in the art to make and use the claimed invention. Certainly, the claims directed to specific compounds and quantities of such compounds are fully disclosed in this application. With regard to the term "allegen", one of ordinary skill in the art wound understand this term to means any substance that causes manifestations of allergy.

The Examiner is hereby requested to reconsider his rejections under 35 U.S.C. 112, first paragraph.

With regard to the rejection of claims 3, 4, 10 - 18 and 26 - 32, appropriate amendments have been made to eliminate the first, third, fourth, and seventh objections set out in the rejection. As for the statement "enabling release of the peptides and other chemical substances in independent manner at galenic level" in claim 3, it is not understood why this claim is ambiguous because the specification does not define what is meant by galenic level and which chemical substances and peptides are being released. First, one of ordinary skill in the art would understand what is meant by the term "galenic level" and which chemical substances and peptides are being released.

The objection to claim 28 is not understood by Applicants. Applicants hereby ask the Examiner to amplify on this objection.

With regard to the objection to claim 29, the specification does not need to define terms which would readily be understood by one of ordinary skill in the art. The Examiner is hereby requested to withdraw the objection to claim 29.

Claims 1 - 4, 14, and 26 - 32 have been rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 6,455,686 to McCall et al. It is submitted that the McCall et al. patent does not teach or suggest the subject matter

of the aforementioned claims. The McCall et al patent relates to the identification of proteins, especially of D. Farinae, and their use in diagnostic or therapeutic to identify or desensitize a subject susceptible to an allergic response to mite. The composition disclosed in this patent might be used in conjunction with other compounds able to modify the function of a cell implied in the hypersensible response. These compounds may be anti-histaminics or compounds which lead the immunoglobulin heavy chain class to switch from IgE to IgG. These latter compounds are not inhibitors of the synthesis of histamine. The action of these compounds occurs at the end of the allergy reaction, and not upstream. The IgE link is an antigene situated in the basophile. This link provokes liberation of histamine by degranulation of the histamine grains. This involves a biochemical reaction which has nothing to do with the inhibition of the synthesis of histamine. Therefore, the McCall et al. patent does not disclose the combination of compounds set out in claim 1 and the other subject matter set forth in claims 2 - 4, 14, and 26 - 32.

Claims 1 - 4, 10 - 13, and 15 - 18 were rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,455,686 in view of U.S. Patent No. 4,302,458, U.S. Patent

No. 6,258,816 or U.S. Patent No. 5,827,852, or U.S. Patent No. 6,319,513. It is submitted that the proposed combination of references, assuming one of ordinary skill in the art would combine them in the manner suggested by the Examiner, does not teach or suggest the claimed invention. In particular, none of the patents teach or suggest the combination of compounds set forth in claim 1. The aforementioned comments about the '686 patent are repeated herein by reference. The '458 patent relates to the use of phtalidyl-isoquinolines derivates, of Noscapine type, to treat allergic conditions. The activity of these compounds is comparable to the tritoqualine inhibitor. The '458 patent would not lead one to arrive at the compositions of the present invention.

The '816 patent relates to an anti-allergic composition comprising Cetrizine. Cetrizine is a histamine antagonist. Nimesulide stabilizes the mast cells, which would prevent the histamine secretion. In a normal situation, histamine can be found in all tissues, and especially in mastocytes. Histamine is stocked in vesicles, called granules in basophiles. By stabilizing the mast cells, it is meant to avoid the fusion of the histamine vesicles with the membrane and the consequent liberation of the histamine stock. This action is really

downstream compared to the action of an inhibitor of the synthesis of histamine. It is not understood by Applicants how this patent in combination with the others would lead one of ordinary skill in the art to the claimed invention.

The '852 patent relates to a pharmaceutical composition containing anti-histaminic compounds for treating allergies. Here again, it is not understood what in this patent would lead one of ordinary skill in the art to the compositions of the claimed invention.

The '513 patent also discloses a pharmaceutical composition containing anti-histaminic compounds for treating allergies. Here again, it is not understood what in this patent would lead one of ordinary skill in the art to the compositions of the claimed invention.

At best the Examiner has found individual materials used in the compositions of the present invention. Using the blueprint provided by Applicants, the Examiner then attempts to piece them together to arrive at the claimed invention. This is nothing more than a classic hindsight rejection. It is submitted that none of these references recognizes the invention made by Applicants and most certainly would not lead one of ordinary skill in the art to make and use the claimed compositions.

None of the cited and applied references would teach or suggest the combination of claim 1. None of the cited and applied references descries the fact of simultaneously inhibiting the synthesis of histamine and competing histamine fixation. None of the cited and applied references describes or suggests acting at the different levels of the allergic reaction chain as described in the instant application. It must be understood that inhibiting the liberation of histamine is really different from inhibiting the synthesis of histamine and that this is a key point that distinguishes the pending invention from the cited and applied prior art.

For the foregoing reasons, the instant application is believed to be in condition for allowance. Such allowance is respectfully solicited.

Should the Examiner believe an additional amendment is needed to place the case in condition for allowance, the Examiner is hereby invited to contact Applicant's attorney at the telephone number listed below.

No fee is believed to be due as a result of this response. Should the Commissioner determine that a fee is

due, he is hereby authorized to charge said fee to Deposit Account No. 02-0184.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: "Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313" on June 24, 2003.

Nicole Motzer

VERSION WITH MARKINGS TO SHOW CHANGES MADE

Claims 1 - 4, 10 - 18, and 26 - 32 have been amended as follows:

1) (Amended) [Anti-allergic] An anti-allergic pharmaceutical composition containing at least two active agents chosen among : (i) one allergen, (ii) one antihistamine compound, (iii) one inhibitor of histamine synthesis, said active agents being associated in said composition with a pharmaceutically acceptable vehicle.

2) (Amended) [Anti-allergic] The anti-allergic pharmaceutical composition according to claim 1, containing (i) at least one allergen and (ii) at least one antihistamine compound, and optionally (iii) at least one inhibitor of histamine synthesis, in a pharmaceutically acceptable vehicle.

3) (Amended) [Anti-allergic] The anti-allergic pharmaceutical composition according to any of claims 1 or 2, [characterized in that it] wherein said composition contains (i) at least one allergen and (ii) at least one antihistamine compound, in a pharmaceutically acceptable

vehicle, enabling release of the peptides and other chemical substances in independent manner at galenic level.

4) (Amended) [Pharmaceutical] A pharmaceutical composition according to any of claims 1 to 3, [characterized in that] wherein the allergen is chosen from among the major antigens or mixture of major antigens of acarids able to induce an immune reaction.

10) (Amended) [Pharmaceutical] The pharmaceutical composition according to any of [the preceding] claims 1 - 4, [characterized in that] wherein the antihistamine compound is chosen from the group comprising: brompheniramine, cetirizine, fexofenadine, cyproheptadine, dexchlorpheniramine, hydroxizine, ketotifene, loratidine, mequitazine, oxotomide, mizolastine, ebastine, astemizole, carbinoxamide, alimemazine, buclizine, cyclizine hydrochlorate, doxylamine.

11) (Amended) [Anti-allergic] The anti-allergic pharmaceutical composition according to any of claims 1 or 2, [characterized in that it] wherein said composition contains at least one antihistamine compound and at least one inhibitor of histamine synthesis, said compound[s]

being associated in said composition with a pharmaceutically acceptable vehicle.

12) (Amended) [Pharmaceutical] The pharmaceutical composition according to claim 11, [characterized in that] wherein the inhibitor of histamine synthesis is an inhibitor of histidine decarboxylase.

13) (Amended) [Pharmaceutical] The pharmaceutical composition according to claim 12, [characterized in that] wherein the inhibitor of histidine decarboxylase is tritoqualine.

14) (Amended) [Pharmaceutical] The pharmaceutical composition according to any of claims 1 [to] - 4 and 10, [characterized in that it] wherein said composition contains a quantity of allergen of the order of 1 to 1500 µg[, and advantageously from 10 to 150 µg].

15) (Amended) [Pharmaceutical] The pharmaceutical composition according to any of [the preceding] claims[, characterized in that it] 1 - 4 and 10 - 14, wherein said composition contains a quantity of antihistamine compound

of the order of 1 to 2000 mg[, and advantageously from 5 to 200 mg].

16) (Amended) [Pharmaceutical] The pharmaceutical composition according to any of claims 1 [to] - 4 and 10 - 15, [characterized in that it] wherein said composition contains an inhibitor of histamine synthesis.

17) (Amended) [Pharmaceutical] The pharmaceutical composition according to claim 16, [characterized in that it] wherein said composition contains a quantity of [inhibitor of histamine synthesis] antihistamine compound of between 1 and 2000 mg.

18) (Amended) [Pharmaceutical] The pharmaceutical composition according to any of claims 11 to 13, [characterized in that it] wherein said composition contains from 5 to 200 mg of an antihistamine compound and from 10 to 300 mg of an inhibitor of histidine decarboxylase [such as tritoqualine].

26) (Amended) [Pharmaceutical] The pharmaceutical composition according to any of [the preceding] claims[, characterized in that it] 1 - 4 and 10 - 18, wherein said

composition permits the TH2/TH1 switch and reduction of the allergic reaction both on the upstream phase (IgE synthesis) and on the downstream phase (synthesis and release of histamine).

27) (Amended) [Pharmaceutical] The pharmaceutical composition according to any of [the preceding] claims[, characterized in that it] 1 - 4, 10 - 18 and 26 wherein said composition is released in the form of a transcutaneous patch to allow better access of the allergens used and/or their epitopes to the antigen-presenting cells.

28) (Amended) [Pharmaceutical] The pharmaceutical composition according to any of [the preceding] claims [characterized in that it] 1 - 4, 10 - 18, 26 and 27, wherein said composition is released in mucosal, eye lotion, nasal spray or bronchial form.

29) (Amended) [Pharmaceutical] The pharmaceutical composition according to any of [the preceding] claims [characterized in that it] 1 - 4, 10 - 18 and 26 - 28, wherein said composition is released in a galenical form

with programmed mucosal or sublingual and secondarily *per os* disintegration.

30) (Amended) [Pharmaceutical] The pharmaceutical composition according to any of [the preceding] claims 1 - 4, 10 - 18 and 26 - 29 for the preparation of a medicinal product intended to treat or prevent allergic hypersensitive reactions.

31) (Amended) [Pharmaceutical] The pharmaceutical composition according to any of [the preceding] claims 1 - 4, 10 - 18 and 26 - 30 for the preparation of a medicinal product intended to treat or prevent allergic asthma, allergic rhinitis, atopic and allergic eczema.

32) (Amended) [Pharmaceutical] The pharmaceutical composition according to any of [the preceding] claims 1 - 4, 10 - 18 and 26 - 31 for the preparation of a medicinal product intended to treat or prevent allergic symptoms in children, infants and adults.

The abstract has been amended as follows:

[ABSTRACT] ABSTRACT OF THE DISCLOSURE

The present invention relates to an anti-allergic pharmaceutical composition containing at least two active agents chosen from among : (i) one allergen, (ii) one antihistamine compound, and (iii) one inhibitor of histamine synthesis[, said]. The active agents [being] are associated in [said] the composition with a pharmaceutically acceptable vehicle.

ANTI-ALLERGIC PHARMACEUTICAL COMPOSITION CONTAINING AT LEAST ONE ALLERGEN AND AT LEAST ONE ANTIHISTAMINE COMPOUND

BACKGROUND OF THE INVENTION

(1) Field of the Invention

The present invention relates to new pharmaceutical compositions for the prevention and treatment of allergies. Allergies are a scourge which affects 25% of the world's population. This number is on the increase in connection with growing environmental toxicity (dust, food, motor vehicles). In addition, a person's risk of suffering from allergy is increased if there is a previous family history of allergy.

(2) Prior Art

The biological mechanism of allergies may be described as an abnormally amplified reaction to the entry of an allergen into the body. The following events account for the reaction:

- identification of the allergen by the body,

- secretion of cytokines in response to allergen penetration,

- conversion of Th1 cells into Th2 cells, with the production of clones specific to the antigen,

- the Th2 cells synthesize interleukins 4 and 13, responsible for aggravation of the allergic symptoms through an upsurge in IgE synthesis

- the terminal phase of the reaction is the release of histamine and serotonin having a recruiting effect on the Th2 clones.

- toxic and inflammatory self-maintaining reaction, even without any antigen stimulation.

The antigen-presenting cells (APCs: macrophages, dendritic cells, B-lymphocytes) take part in the reaction of hypersensitivity through basic cell cooperation carrying the immune reaction further. Allergies belong to the nonself class of [defence] defense mechanisms. The main allergens are acarids (dust mites) (80%) and pollens (20%).

The self-stimulating reactions of specific APC clones have an effect on the general rate of release of histamine and serotonin leading to an aggravation of the general clinical symptomatology.

The recruitment level of new Ige-secreting cells is thereby increased, facilitating the explosion of clinical signs when a new allergen penetrates inside the body. This can be seen in atopic persons in whom allergic reactions are severe owing to the high level of Th2 clones promoting the synthesis of IgE.

The general reaction observed subsequent to the penetration of the new allergen is not due to its toxicity but simply to the fact that the triggering level of allergic phenomena is very low, helped by other [sensitisations] sensitizations.

An allergy is a reaction due to hypersynthesis of IgE immunoglobulins. The inflammatory reaction chiefly affects the respiratory and ENT spheres, with pathological [focalisation] focalization at the nose, lungs and skin. Pathologies associated with the allergy are invalidating and suffer from the lack of efficacy of conventional treatment. There is no preventive strategy and curative means are insufficient or ill used.

The usual treatment of allergic disease consists, during a first phase, of identifying the allergen responsible[:] such as dust mites, pollen, [mould] mold, or food. The second phase comprises removal measures. The third phase or treatment phase focuses on the target organ which appears to be symptomatic[:] e.g., ENT treatment for rhinitis, anti-asthmatic treatment if the affected sphere is respiratory, dermatological treatment if the affected areas are skin areas.

In the event of failure of the preceding measures, individual or complementary treatment may be offered through the choice of a specific immunotherapy [(], i.e. specific pollen, specific acarid, specific [mould)] mold. The complexity of the treatment instituted makes it

difficult to follow. A succession of treatments is a patent factor of failure.

SUMMARY OF THE INVENTION

The purpose of the present invention is precisely to offer new means of treating allergies that are both preventive and curative.

This purpose is achieved by treating the two main sides of the immune reaction: [-] firstly, the upstream part of the immune response which, after presenting the antigen to the APCs, leads to increased synthesis of the IgEs responsible for the self-recruiting of the immunity cells, and [-] secondly, the downstream side of the immune response which leads to release of the preformed mediators, essentially histamine, responsible for the final clinical outcome.

The optional combined use of an inhibitor of histamine synthesis makes it possible to reduce the concentration of the latter and therefore to improve the therapeutic efficacy of the pharmaceutical composition according to the invention.

The present invention concerns [a] an anti-allergic pharmaceutical composition containing at least two active agents chosen [among :] from among: (i) one allergen, (ii) one antihistamine compound, and (iii) one inhibitor of histamine synthesis, with said active agents being associated in said composition with a pharmaceutically acceptable vehicle.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT(S)

[Consequently, the] The subject of the invention is more particularly an anti-allergic pharmaceutical composition containing (i) at least one allergen and (ii) at least one antihistamine compound, and optionally (iii) at least one inhibitor of histamine synthesis, in a pharmaceutically acceptable vehicle.

A first preferred form of an anti-allergic pharmaceutical composition according to the invention contains (i) at least one allergen and (ii) at least one antihistamine compound, in a pharmaceutically acceptable vehicle, enabling release of [the] peptides and other chemical substances in an independent manner at galenic level.

Advantageously, [said] the allergen is chosen from among the major antigens or a mixture of major antigens of acarids able to induce an immune reaction. [Indeed, the] The research conducted within the scope of the invention consisted of using ubiquitous antigens of acarids. These antigens are present in substantial quantity in the environment and are the cause of the development of allergic reactions in the world. Two acarids, *D. Pteronyssinus* (DP) and *D. Farinae* (DF) are the most represented in the world environment.

The present invention most particularly gives consideration to a cystine protease as an allergen, the carrier of antigenicity which is [90 %] 90% identical for these two acarids. The epigenic and amino acid sequences of the cystine protease of *D. Pteronyssinus* (DP) are shown in the list of appended sequences given respectively under numbers SEQ ID [NO :] NO: 1 and SEQ ID [N0 :] NO: 2.

The allergens used in the compositions of the invention may either be extracts obtained from crude biological material, or wholly or partly purified proteins optionally produced by genetic engineering or by peptide synthesis.

Therefore the invention further concerns, as an allergen, the peptide epitopes of cystine protease. Three epitopic parts have been identified which form triggering agents for the immune response. These are the three peptides with the following sequences:

RMQGGCGSCN (SEQ ID [NO :] NO: 3)

QPNYHAVNIV (SEQ ID [NO :] NO: 4)

WTVRNSWDT (SEQ ID [NO :] NO: 5)

and their possible analogues.

The sequences of the protein epitopes cited above may contain primers and supplementary amino acid sequences or substitutions facilitating their adhesion to the Major Histocompatibility Complex (MHC).

The invention gives special consideration to pharmaceutical compositions containing at least one of these peptides as an allergen.

These peptide epitopes are strictly identical in DF and DP, and in other acarids, since they are carriers of the enzyme function of cystine protease. Their lipophilia, and the fact that they tolerate the enzyme function, account for the fact that these epitope parts are constant from one species of acarid to another and that they are the site of a general immune response.

The use of these parts, either in the form of cycled proteins, or in epigenic form, or even in their RNA form,

[must] induce tolerance to the natural antigen and reduce the general level of the immune response upstream.

[Cyclising] Cyclizing the epitopes and/or inclusion of the epigenic patterns in a longer sequence makes it possible to improve the [presenting] presentation of the antigens to the T-lymphocytes. This improved presentation will allow presentation of the antigens and epitopes to the MHC and thereby trigger the immune tolerance response. The antigens must previously be rearranged by the APCs. The simple epitopic form does not allow rearrangement by the APCs since, as a general rule, only a protein longer than 10 amino acids may be cut and presented by the APCs to the T-lymphocytes.

These peptides may be associated with any pharmaceutically acceptable vector, for example, of phospholipid type [for example].

If epigens are involved, the latter may be primed by the following nucleotide sequence: 5'GCGGCGGCG 3' (SEQ ID [NO :] NO: 6).

The controlled reaction of the TH2/TH1 switch induced by this protein, or its epigen, may also be achieved using other methods, in particular with the nucleotide primers according to the following sequence 5'TGAGCGGCGGCG 3' (SEQ ID [NO :] NO: 7), and using any other method allowing upstream control of the TH2/TH1 switch.

It is therefore possible to integrate the epigens corresponding to the epitopes of DP/DF with a nucleotide primer sequence of sequence (SEQ ID [NO :] NO: 7) by alternating said sequence (SEQ ID [NO :] NO: 7) and an

epitope [such] so as to integrate the three major epitopes of DP/DF, either together or separately.

The integration of the epitopes together leads to obtaining a group made up of a first nucleotide primer sequence (SEQ ID [NO :] NO: 7), a first major epitope, a second nucleotide primer sequence (SEQ ID [NO :] NO: 7), a second major epitope, a third nucleotide primer sequence (SEQ ID [NO :] NO: 7), and a third major epitope.

The integration of epitopes separately leads to mixing three groups each made up of a nucleotide primer sequence (SEQ ID [NO :] NO: 7) and a major epitope. This integration of the epitopes with a nucleotide primer sequence according to the following sequence (SEQ ID [NO :] NO: 7) [must improve] improves the efficacy with which the DP/DF epigens are presented to the T-lymphocytes. With this improved presentation, the DP/DF epigens will stimulate the TH1 switch and, therefore, reduce the level of the allergic response.

The use [firstly] of these epitopes, or of a solution enabling the TH1/TH2 switch, such as the nucleotide primers of sequence (SEQ ID [NO :] NO: 7), and [secondly] their association with an antihistamine compound, and optionally with an inhibitor of histamine synthesis, provide an efficient, innovative solution for the prevention and treatment of allergies.

Consequently, the compositions of the present invention comprise an efficient quantity of at least one allergen, such as defined above, without predicting the role of this allergen in the patient's symptomatology.

With this approach, it is possible to have global access to the allergic illness without giving

consideration to the specificity of the allergen. Indeed, with the composition of the invention, it is possible to treat a level of immune reactivity and not to propose a specific immunotherapy.

The use of the allergen, under the different forms described above, in the compositions of the present invention means that it is possible to induce tolerance to the natural antigen and to reduce the general level of immune response upstream. However, as mentioned previously, the allergen cannot alone cure the allergy since the toxic, inflammatory terminal reaction subsists, which is self-maintaining without antigen stimulation. This reaction must also be treated by blocking the terminal phase of the allergy. Blocking the histamine receptors is the main effector mechanism. This blocking must be made over a time interval that is sufficiently long for there to be a negative feedback on the synthesis of these receptors. Antihistamines are anti-receptor molecules of choice to block this terminal reaction. Therefore, the compositions of the invention, in addition to the allergen, contain an antihistamine compound, and, optionally, an inhibitor of histamine synthesis.

[As] Suitable antihistamine compounds[, mention] may be made of: brompheniramine, cetirizine, fexofenadine, cyproheptadine, dexchlorpheniramine, hydroxizine, ketotifene, loratidine, mequitazine, oxotomide, mizolastine, ebastine, astemizole, carbinoxamide, alimemazine, buclizine, cyclizine hydrochlorate, and/or doxylamine.

As indicated above, the allergy is also accompanied by increased synthesis of histamine, which also causes self-maintaining of the terminal inflammatory reaction. This histamine synthesis may possibly be controlled, in order to improve the efficacy of the previously proposed pharmaceutical composition. This control has recourse to the inhibition of histamine synthesis. Consequently, the compositions of the invention contain an efficient quantity of an antihistamine compound which may optionally be associated with an inhibitor of histamine synthesis. Therefore, blocking of the terminal histamine effector mechanisms will provide efficient control over the final cascade of the allergic reaction. The terminal route for the synthesis and stimulation of histamine receptors must therefore be blocked in global manner for the composition to have improved efficacy.

A particular form of implementation of the invention consists in [a] an anti-allergic pharmaceutical composition containing at least one antihistamine compound and at least one inhibitor of histamine synthesis, with said compounds being associated in said composition with a pharmaceutically acceptable vehicle.

As inhibitors of histamine synthesis, mention may be made of an inhibitor of histidine decarboxylase [as] such as tritoqualine.

By preventing histamine synthesis, the inhibitor of histidine decarboxylase increases the efficiency of the composition in its action on the downstream side of the allergies' biological mechanism by complementing the antihistamine compound.

The compositions of the invention provide a new allergen approach providing preventive vaccination against the development of allergic illnesses. The [objective being] object is to restore a silent [defence] defense homeostasis to the body in relation to its environment.

The compositions of the present invention contain a quantity of allergens [in] on the order of 1 to 1500 µg and, advantageously, from 10 to 150 µg. Concerning the peptides, each one is advantageously present in proportions in the [region] range of 1 to 1500 µg so as to slow down the immunological response leading to increased IgE synthesis.

The antihistamine compound is present in the compositions of the invention in a proportion [of] on the order of 1 to 2000 mg.

In the case of a composition according to the invention containing [a] an antihistamine compound and an inhibitor of histamine synthesis, these compounds are present in a proportion [of] on the order of: [-] 5 to 200 mg of antihistamine compound, [-] and 10 to 300 mg of an inhibitor of histidine decarboxylase [as] such as tritoqualine.

The compositions of the present invention may be presented in either a form for transdermal application, [for example] such as an ointment for children, a form for oral administration, [for example] such as a slow release product, or in gastro-resistant tablet form or gum form. They may also be in spray or eye lotion form,

or galenic forms with programmed mucosal and secondarily *per os* disintegration.

[Therefore the] The different compositions of the invention can be administered by several routes chosen in accordance with the patient's pathological profile and age. For children, [the] they can be administered in patch form, syrup form or tablets to be dissolved in the mouth. [The other] Other forms, such as eye lotion or injection may also be used. In adults, all galenic forms can be contemplated.

The [advantage] advantages of a coupled form [also provides] include simplicity of treatment, patient compliance with the simplified treatment, and [therefore] a more successful outcome.

This solution also makes it possible to prevent the allergic illness and not only patent pathological conditions. Children of allergic parents could be the major target of this preventive treatment. The result would be shorter hospital stays, fewer antibiotic treatments, and improved quality of life. Indeed the TH2/TH1 switch must occur as early as possible in order to be effective, since in infants it is the TH2 route which predominates, and is responsible for hyper-response to the environment. The TH2/TH1 switch must occur early for its duration to be as long as possible, since antigenic stimulation by the antigens of the environment (e.g. dust mites and bacteria) are stimulators of the TH2 route.

[Therefore the] The pharmaceutical composition of the present invention is particularly useful for the

preparation of a medicinal product intended to treat allergic hypersensitive reactions.

Advantageously, the pharmaceutical composition of the present invention is in a galenic form with programmed mucosal or sublingual and secondarily *per os* disintegration.

The pharmaceutical composition of the present invention is also useful for the preparation of a medicinal product intended to treat or prevent allergic hypersensitivity reactions, and to treat or prevent allergic asthma, allergic rhinitis and atopic and allergic eczema.

Finally, the pharmaceutical composition of the present invention is particularly useful for the preparation of a medicinal product intended to treat or prevent allergic symptoms in children, infants, and adults.

Other advantages and characteristics of the invention will become apparent on reading the clinical observations made in the treatment of allergic patients as recorded in the table given below.

These observations were made on approximately one hundred patients who were given a composition of the invention associating at least one allergen and an antihistamine compound.

Patient age ranged from 7 to 60 years. They all were presented with at least one positive dust mite or pollen

prick test, and symptomatology of rhinitis or asthma of at least one year's onset.

The pathological profile of the patients was classified according to the following typology comprising three descriptive categories: inflammation, secretion and the figured element.

[-] Only clinical examination was used to classify inflammation. It was considered that there was inflammation if examination of the mucosa or target organs showed redness confirming an inflammatory phenomenon,

[-] Secretion concerned the observation of an exudate whether purulent or non-purulent affecting a target organ (e.g. mucosa, skin, etc…).

[-] The figured element concerned a change in the structure of the organ under consideration, which may occur in several pathological forms. Consideration was only given to the existence of a change without going into the detail of this change.

The grading of pathological severity used a scale of 1 to 4 measuring intensity as a fraction e.g. 1/4 or 1/2, or a whole number.

[Therefore, according] According to this grading, an assessment of 1/4 denotes target organ impairment of between 0 and less than 1/4. An assessment of 1/2 denotes target organ impairment of between 1/4 and one half; an assessment of 3/4 denotes target organ impairment of more than one half and less than 3/4; an assessment of 1 denotes impairment of more than 3/4.

A first category of target organs was graded according to this typology. It comprises the eyes, nose, pharynx, larynx and the skin.

In respect of the lungs, the rating used the results of functional respiratory investigation expressed as a percentage relative to the normal value (using an international classification method taking into account age and size in particular).

The patients were given a follow-up with at least one consultation at 2 months, 8 months, 12 months, 24 months. The course of the treatments followed and the number of units taken were [analysed] analyzed.

Table [1] I below gives a clear indication of the very positive results obtained after a treatment time of approximately 8 months. A distinct improvement was noted in the pathological condition of the patients, with a drop in the overall clinical score for severity falling from an average value of 9.56 to 2.47, the standard deviation decreasing from 1.15 to 0.53, confirming the efficacy of the treatment in all patient age and sex groups. The mean number of affected target organs fell from 3.69 to 1.73, while the standard deviation in the number of target organs affected was reduced from 0.49 to 0.41.

Table I

					Initial consultation		3rd consultation after 8 months' treatment	
Patient reference	Sex	Date of birth	Date of initial consultation	N° of tests +	N° of target organs affected	Total clinical score	N° of target organs affected	Total clinical score
1	M	1964	1996	3	3	7	2	2
2	F	1936	2000	4	3	6	1	2
3	F	1944	1993	8	4	10	2	2
4	F	1974	1997	8	4	9	1	3
5	F	1950	1997	8	4	9	2	3
6	M	1960	1997	7	4	8	1	2
7	F	1944	1996	4	3	6	2	2
8	F	1963	1993	4	5	10	1	2
9	M	1988	1993	7	4	8	2	2
10	M	1991	1993	3	4	9	1	2
11	M	1971	2000	6	3	9	1	2
12	M	1948	2000	3	4	9	1	2
13	M	1929	2000	3	3	7	2	2
14	M	1953	1999	5	4	9	1	1
15	F	1932	1994	10	4	10	1	2
16	F	1934	1996	8	6	11	2	2
17	F	1982	1993	5	4	10	2	2
18	F	1968	1994	4	4	10	2	2
19	M	1996	1996	4	4	10	1	3
20	F	1991	1997	5	4	10	2	3
21	F	1990	1996	7	3	8	1	2
22	F	1949	2000	4	4	8	2	3
23	M	1995	2000	3	2	6	1	2
24	F	1961	1994	8	3	8	1	2
25	M	1987	1994	7	4	9	2	3
26	F	1991	1995	8	3	8	1	2
27	M	1967	1994	7	3	9	2	2
28	M	1989	1994	7	4	9	2	3
29	M	1947	1999	5	4	9	2	2
30	F	1920	1999	2	3	8	1	2
31	F	1963	1997	6	4	9	2	2

					Initial consultation		3rd consultation after 8 months' treatment	
Patient reference	Sex	Date of birth	Date of initial consultation	N° of tests +	N° of target organs affected	Total clinical score	N° of target organs affected	Total clinical score
32	M	1979	1998	4	4	9	1	2
33	F	1983	2000	3	3	8	2	2
34	M	1996	1999	7	4	8	2	2
35	F	1946	1995	7	3	8	2	3
36	F	1958	1995	5	4	10	2	2
37	F	1946	1997	6	4	11	2	2
38	F	1965	1993	3	3	9	1	2
39	M	1973	2000	7	4	9	2	2
40	M	1957	1995	5	4	9	2	2
41	F	1942	1995	8	4	9	2	2
42	F	1933	1999	4	3	9	1	3
43	F	1959	1999	4	3	8	2	3
44	F	1965	1999	3	4	10	2	2
45	F	1944	1999	3	4	10	2	3
46	F	1942	1996	6	4	11	1	3
47	F	1948	1997	6	4	11	2	3
48	F	1963	1999	4	4	10	2	2
49	M	1981	1999	5	4	12	2	2
50	M	1995	2000	5	4	12	2	2
51	M	1989	1999	5	4	10	2	2
52	M	1997	1998	4	4	10	2	3
53	F	1997	1998	5	4	9	1	3
54	F	1995	1997	4	4	10	2	3
55	F	1984	1993	3	3	9	1	2
56	M	1969	1996	10	4	12	2	3
57	M	1951	1996	11	4	11	2	2
58	M	1992	1997	5	4	11	2	3
59	M	1975	1994	4	3	9	1	2
60	M	1977	2000	5	4	12	2	3
61	M	1989	1993	5	4	12	2	3
62	M	1994	1998	8	4	11	2	3
63	F	1993	1998	7	4	10	2	2
64	F	1988	1993	3	3	9	2	3

					Initial consultation		3rd consultation after 8 months' treatment	
Patient reference	Sex	Date of birth	Date of initial consultation	N° of tests +	N° of target organs affected	Total clinical score	N° of target organs affected	Total clinical score
65	F	1940	1999	4	4	11	2	2
72	F	1951	2000	6	4	11	2	3
73	F	1956	1999	5	4	11	2	3
74	M	1982	1994	4	3	9	2	3
75	F	1944	1998	3	4	12	2	2
76	F	1992	1997	7	3	9	2	3
77	M	1997	1993	4	3	9	1	3
78	F	1955	1997	5	4	10	2	3
79	F	1996	1999	4	3	8	2	3
80	F	1936	1993	5	4	10	1	2
81	M	1949	1998	5	3	10	2	2
82	M	1966	1993	4	3	9	2	2
83	F	1963	2000	5	4	10	1	2
84	F	1954	1993	5	4	11	2	2
85	F	1995	2000	4	3	9	2	3
86	M	1988	1994	6	3	8	2	2
87	F	1969	1997	6	4	9	2	3
88	M	1963	1993	5	4	9	2	2
89	M	1994	1998	7	4	10	1	3
90	F	1992	1997	6	3	9	3	3
91	M	1988	1999	6	4	11	2	3
92	M	1955	1993	6	4	11	2	3
93	M	1944	1996	7	4	13	2	3
94	M	1986	1994	6	4	12	2	3
95	M	1954	1996	6	4	11	2	3
96	F	1989	1993	6	4	12	2	2
97	M	1965	1995	6	3	8	2	3
98	M	1986	1994	4	3	9	2	4
99	F	1956	1995	4	4	10	2	3
100	F	1944	1993	2	3	9	1	3
101	F	1995	1998	5	3	9	2	4
102	M	1960	1996	3	3	8	2	3
103	F	1928	1995	6	4	10	2	3

Table II below gives the mean clinical score and the standard deviation in the scores obtained.

Table II

			INITIAL VISIT	VISIT AT 8 MONTHS
MEAN CLINICAL SCORE			9.56	2.47
STANDARD DEVIATION IN SCORES			1.15	0.53

Table III below illustrates the average number of target organs affected and the standard deviation in the number of target organs affected.

Table III

			INITIAL VISIT	VISIT AT 8 MONTHS
MEAN N° OF AFFECTED TARGET ORGANS (T.O.)			3.69	1.73
STANDARD DEVIATION IN N° AFFECTED T.Os.			0.49	0.41